REMARKS

Claims 37-45 will remain in the application after entry of the Preliminary Amendment. The previous claims have been canceled and replaced with a new set of claims, which clarify the invention. These claims were suggested by the Examiners and were discussed in a telephone interview February 21, 2008. It is believed that the new claims are in condition for allowance.

On page 24, Example 7 has been changed to "Example 8", to correct an obvious error. Amendments to pages 6, 10, and 15 have been made in response to the Examiner's suggestion that new matter may have been entered.

The present invention is novel in that monoclonal antibodies were raised from purified uristatin, which is a UTI that has only recently been identified in humans by a research team under the direction of the first-named applicant. The new monoclonal antibodies bind lower molecular weight UTIs. As stated at page 5, line 32 to page 6, line 3, "These monoclonal antibodies are characterized by their ability to allow direct or indirect measurement of urinary trypsin inhibitors ... in the presence of other common proteins in urine or serum ... and non-inhibitory urinary trypsin inhibitors ... such as I-α-I and P-α-I."

Election/Restrictions

The Examiner has made the restriction requirement final on the basis that Trefz et al teach monoclonal antibodies raised from purified UTI, and therefore a monoclonal antibody for detecting UTI cannot be a special technical feature. The Applicants disagree. Trefz et al used HI-30, which is the same or closely related to "bikunin", having a molecular weight of about 33 kDa. The Applicant's monoclonal antibodies were raised from purified "uristatin", which has a molecular weight of about 17 kDa. Thus the monoclonal antibodies of the application are novel and do not correspond to Treftz' monoclonal antibodies. They are useful in detecting uristatin and its fractions, which have been designated as uristation-1 and uristation-2. Thus, Groups I and II do relate to a single general inventive concept, contrary to the Examiner's position.

Priority

The Examiner contends that the provisional parent of the present application and the international application "fail to provide sufficient written support or enablement in the

manner provided by the first paragraph of 35 U.S.C. 112 for the newly added limitations", which referred to a lack of cross-reactivity with P-α-I and I- α-I pro-inhibitors. Although the new claims do not refer to cross-reactivity, the Applicants have support from the specification of the international application, which was published in the US as 2007/0020683 A1.

The Examiner has remarked that the entire genus of pro-inhibitors was not sufficiently disclosed. While this concern has been obviated by the above amendments, the pro-inhibitors P-α-I and I- α-I are specifically included in Tables 3 and 4 of the specification and defined at [0037] in the published application or page 8, line 14-18. Thus, these pro-inhibitors are sufficiently described.

Although the corrections made to the specification in the Preliminary Amendment filed 4/6/2006 were not included in the published application, the Examiner's comments suggest that they were entered and constitute new matter. These amendments were discussed in detail in the Preliminary Amendment. However, in the above amendments the concerns about new matter should have been avoided, since the amendments mainly remove material from the text.

The amendments at page 6 are supported by the SELDI testing reported in Table 3 and 4. Therefore, correction of the original description, which was based on less-specific ELISA analysis, does not constitute new matter, but only states what the SELDI tests found. Reference to the binding of named monoclonal antibodies has been removed.

The amendment at page 10 deletes incorrect information regarding the immunogen composition used in preparing the monoclonal antibodies. The specific composition data was removed and replaced with the immunogen lot number, which was shown to have been used in the declaration of Michael Pugia, Ph.D, which was submitted with the preliminary amendment of April 6, 2006. This immunogen was substantially uristatin, which supports referring to the resulting monoclonal antibodies as being produced from purified uristatin.

The amendment made at page 15, line 15 et. seq. was made to avoid misunderstanding of the original text and to clarify the point being made.

The amendment at page 15, line 24 et seq. also was made to avoid appearing to contradict the previous sentence found in the original text.

In summary, corrections were being made to avoid errors or inconsistencies in the application as originally filed. The correction to the immunogen was an error of fact which

could not be allowed to remain in the application. None of these changes should be considered "new matter" if properly understood.

Rejections under 35 U.S.C. 112, Second Paragraph

Claim 19 has been rejected again as indefinite, with regard to the term "defined herein". Claim 19 has been canceled and replaced by new claim 43, in which the acronyms have been defined.

Claims 12 and 14-23 have been rejected as indefinite for the use of the term "preferentially bound". This rejection is moot in view of the above amendments, which do not include that term.

"Preferentially bound" is a term of the art. One skilled in the field of immunoassays used to analyze biological samples would understand that the degree of binding of an antibody to a target antigen is measured relative to its binding to related antigens. That is, the antibody is preferentially bound. If not, then the target antigen cannot be identified within the sample being tested. However, it is not usual that binding events are so specific that only the target antigen is identified. Thus, "preferentially bound" is consistent with usage in the field.

The words, "strongly", "preferentially" and similar terms are used throughout the specification in connection with the use of the three monoclonal antibodies that were secreted by certain named hybridomas. Reference is made in the specification to the relative strength of binding among related UTIs. For example:

- "the three monoclonal antibodies...have been found to bind preferably to Uristatin and Uristatin-1 and 2." ([0023] in the published application or page 6, lines 25-26).

- "the monoclonal antibody 421-568 bound strongly to UTI lots #124-111 and #20-120 to a similar degree but only weakly to lot #80-117." ([0061] in the published application or page 15, lines 15-16).

- "the monoclonal antibody 420-5D11 bound strongly to UTI lot #20-120, very weakly to lot #124-111, and did not bind to lot 80-117." ([0062] in the published application or page 15, lines 24-25).

- "the monoclonal antibody 421-365 bound strongly to all UTI lots." ([0063] in the published application or page 16, line 9).

- "those binding events of high affinity, frequency or importance are in bold face as determined by signal – to noise ratios of binding events. The primary binding events are in bold face and underlined. Weak binding events are in plain text." ([0086] in the published application or page 21, lines 7-10).

- "the extent or strength of binding to a given UTI was estimated relative to other UTIs." ([0089] in the published application or page 23, lines 8-9).

- "the primary binding for Mab 421-365 was strong for Uristatin-1 or -2. Uristatin Bikunin, and AMBK and much less strong for THP with no significant pro-inhibitor binding." ([0090] in the published application or page 23, lines 17-18).

- The SELDI results however also demonstrate that all three antibodies strongly bound to several new forms of Uristatin-1 or -2, Uristatin, Bikunin, and AMBK within the expected ranges for each." ([0091] of the published application or page 23, lines 27-29).

- "Cross reactivity studies were done in a competitive format to allow relative binding to be compared." ([0092] in the published applications or page 24, lines 10-11).

In particular, Tables 3 and 4 show the relative binding of the monoclonal antibodies to UTIs within certain molecular weight ranges. As noted at page 21, lines 9-11 "the primary binding events are in bold face and underlined. Weak binding events are in plain text to document variations in the proteins. These represent very weak cross-reactivities of the type that would not impact an immunoassay if properly formatted." That is, the SELDI data shows more extensive binding than is needed in typical assays, such as the ELISA test. However, in the typical assay the weak binding events would not be seen in a well-designed test. Then, the characteristic binding patterns for each monoclonal antibody could be identified as associated with certain diseases.

Claims 12, 14-23, 26 and 33 have been rejected as failing to comply with the written description requirement and for new matter, relating to the reference to "cross-reactivity". Again, the rejection is moot in view of the amendments.

It is important that the monoclonal antibodies are able to identify certain UTI in order to be useful in clinical work. As shown in the specification, polyclonal antibodies can bind many UTI, but without providing a basis for distinguishing among them, and they also bind pro-

inhibitors. Thus, their lack of specificity makes polyclonal antibodies of less value than the monoclonal antibodies of the present application (*see* [0013] in the published application or page 3, lines 17-32). Cross-reactivity to pro-inhibitors is not desirable, particularly in blood analysis as discussed at [0054] in the published application or page 13, lines 22-28. The results of the very sensitive SELDI method (Tables 3 and 4) show that two of the three monoclonal antibodies had no significant binding to either P- α -I or I- α -I pro-inhibitors, while the third monoclonal antibody (568) showed only a weak binding to P- α -I pro-inhibitors. However, as noted on page 21, lines 9-11, such weak binding events "would not impact an immuno-assay if properly formatted". Thus, it should be evident that the specification as originally filed does support the claims limitations relating to the lack of cross-reactivity to P- α -I and I- α -I pro-inhibitors. Furthermore, Table 5 illustrates a cross-reactivity test in which four proteins were tested for cross-reactivity with the three monoclonal antibodies derived from purified uristation. These tests were done with the less sensitive ELISA test used for clinical purposes. Only Mab 420-5 D11 was found to have cross-reactivity, and that only to THP, as recited in Claims 16 and 33.

Claims 12 and 14-23, 26-26 have been rejected as not enabling the correlation of any disease with measured UTIs. These claims have been canceled, thus obviating the rejection. However, those claims or new claims 37-45 do not claim assaying of a biological fluid for a disease as characterized by measuring UTI's. Rather, the claims describe a method of assaying a biological fluid for UTI's using monoclonal antibodies raised from purified uristatin. As the application explains, UTI's have been related to inflammation or infection and may be associated with many diseases. However, the effectiveness of the present monoclonal antibodies compared with other prior art test methods recently has been shown in a 2006 paper authored by a group including several of the Applicants submitted with a previous amendment. More precise correlation of UTIs with specific diseases is anticipated. As there reported, *"New methods now allow the direct measurement of specific forms of uTi with monoclonal antibodies in urine and blood. This is the first report of monoclonal antibodies that do not show an interfering cross reactivity to proinhibitors in blood and THP in urine"*. (*See* page 14, left column).

The last sentence states the novelty and usefulness of the method being claimed. Cross-reactivity with interfering proteins can be avoided, thereby making possible identification of the uristatins in biological samples and potentially, correlation with specific diseases.

Claims 12, 14-23, and 26-36 have been rejected for failing to comply with the enablement requirement in that the biological deposit amendment does not fully comply with 37 CFR 1.801-1.809. Although this rejection has been obviated, it is assumed to apply to new claims 37-45 as well. Therefore, the Applicants and their assignee confirm that, as required by 37 CFR 1.808(a)(2), all restrictions imposed by the depositor on the availability to the public of the deposited materials will be irrevocably removed upon the granting of a patent from this application.

Rejection under 35 USC 102

Claims 12, 20-21 and 25 have been rejected under 35 USC 102(b) as anticipated by Papuashvili et al (US 6,242,197) ("Papuashvili"). This rejection will be discussed as if made to new claims 37-45. The critical difference lies in the type of UTI used to raise antibodies. Papuashvili raised her monoclonal antibodies using an "acidic glycoprotein" having molecular weight of about 44 kDa (see column 3, lines 17-34 and column 5, lines 12-16) and not the purified uristatin of the Applicants. Thus the antibodies of the '197 patent are not inherently the same as those used in the claimed method. The monoclonal antibodies raised from purified uristatin (molecular weight about 17 kDa) are unique in that uristatin was only recently recognized as a fragment of bikunin. These monoclonal antibodies have more specificity, since they are not cross-reactive with higher molecular weight proteins that interfere with assays of UTIs.

The Papuashvili patent defined UTI as being "an acidic glycoprotein" having a molecular weight of about 44kDa. Thus, when the monoclonal antibodies were raised from a material considered to be a UTI, as it was defined, it was assumed that the monoclonal antibodies were binding the same UTI, which was related to the AID's virus. There was no suggestion that individual fractions of urinary trypsin inhibitors were present or distinguished from each other. This is evident from the fact that Papuashvili fails to distinguish between monoclonal antibodies and polyclonal antibodies. Clearly, all forms of UTI were being detected, or were thought to be.

The Examiner mis-applies the general principle that patentability is based on the product rather than the process of making it, i.e., the method used to make monoclonal antibodies. She apparently concludes that the monoclonal antibodies of Papuashvili are the same, in some sense, as those of the Applicants since both were monoclonal antibodies. However, while the Applicants' monoclonal antibodies result from a similar process, it begins

with a different starting material. Thus, the monoclonal antibodies inherently cannot be the same as the Papuashvili. The antibodies would have a different structure, since they derive from a different immunogen.

In her comments, the Examiner also states that "given monoclonal antibodies are highly specific it would be inherent that the reference monoclonal antibody would not have cross-reactivity to P-α-I and I- α-I pro-inhibitors". The Examiner has suggested that the Applicants should show that the Papuashvili's monoclonal antibody does have cross-reactivity to pro-inhibitors. As a practical matter, it should be obvious that duplication of Papuashvili's results is not possible. In Example 1, the patentee merely states that "three monoclonal antibodies were raised against UTI in a manner known per se". While it is assumed that the reference is to bikunin, the composition of the immunogen is unknown, as are the methods used. Furthermore, Papuashvili suggests and claims that polyclonal and monoclonal antibodies provide similar results. However, the Applicants have shown that polyclonal antibodies do react with pro-inhibitors (see Tables 3 and 4). One can conclude that Papuashvili's polyclonal antibodies, being less specific in their binding to UTIs, also would bind pro-inhibitors. Furthermore, it can be shown from other publications that monoclonal antibodies raised from bikumin and other higher molecular weight UTI's do bind to pro-inhibitors. The vague details supplied by the Papuashvili patent do not support the Examiner's assumption that the reference monoclonal antibody would not have cross-reactivity to pro-inhibitors.

The Applicants teach that UTI includes many forms, use a purified fraction containing substantially uristatin to raise monoclonal antibodies, and demonstrate that their monoclonal antibodies bind to several low molecular weight UTIs, which are related to the immunogen used to raise the monoclonal antibodies. Therefore the Applicant's method is not anticipated. Furthermore, it could not be considered obvious from the limited disclosure of the '197 patent. In view of the amendments and the discussion above, the claims are believed to be in condition for allowance. If the Examiner believes that further consideration is needed, she is invited to contact the Applicant's attorney to arrange a telephone interview.

Respectfully submitted,

2/26/08
Date

Harold N. Wells
Reg. No. 26,044
Kelley Drye & Warren LLP
333 West Wacker Drive, Suite 2600
Chicago, IL 60606
Attorney for Applicants
Tel.: (312) 857-2336